

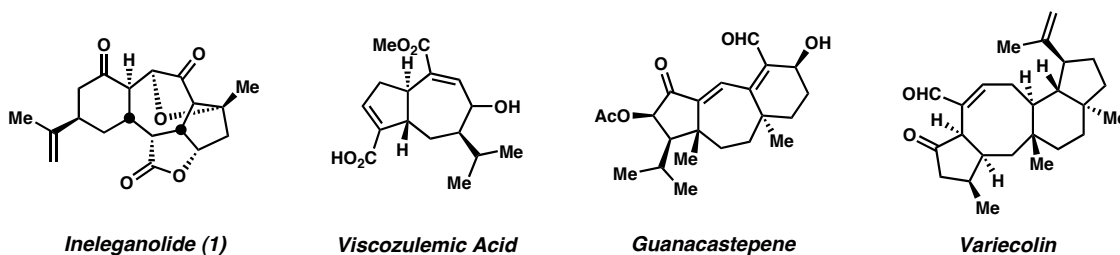
CHAPTER TWO

Polycyclic Natural Products as Inspiration for the Development of the Tandem Wolff/Cope Rearrangement

2.1 Targeting Natural Products Containing Highly Functionalized Seven- and Eight-Membered Rings

As part of a program in the total synthesis of structurally complex natural products, we are interested in developing new methods to form highly functionalized medium-sized rings, such as those found in the [5–7]-, [6–7]-, and [5–8]-fused scaffolds displayed in ineleganolide (**1**), guanacastepene, viscozulemic acid,¹ and variecolin. In particular, the Stoltz group is interested in the development of tandem reactions as a general strategy for synthesis² because of their unique ability to rapidly develop structural complexity.³ Medium-sized rings (7–12 carbons) comprise the structural cores of many bioactive small molecules, but remain difficult to access.⁴ Methods to form medium rings are rendered more challenging by transannular interactions or entropic factors.⁵ Nevertheless, a few synthetic approaches provide access to highly functionalized fused seven-membered rings, including ring fragmentation,⁶ ring expansion,⁷ and cycloaddition⁸ strategies. This chapter provides a full account of a novel thermal rearrangement strategy developed within the Stoltz group: the Wolff/Cope rearrangement.

Figure 2.1.1 Natural products containing [5–7]-, [6–7]-, and [5–8]-fused scaffolds

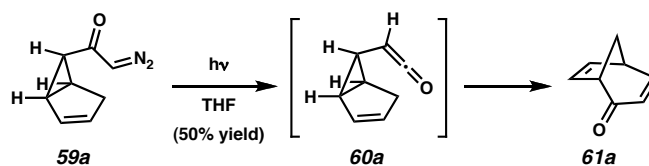


2.2 The Wolff/Cope Rearrangementⁱ

2.2.1 Toward Cycloheptadienones — Cyclopropane Strain Release

Our interest in forming medium rings was piqued by an isolated report of a Wolff rearrangement followed by a ketene-Cope reaction, published in 1965.⁹ Freeman and Kuper observed the rearrangement of [5,3]-fused α -diazoketone **59a** to [3.2.1]-bridged bicycle **61a**, presumably via ketene **60a**.

Scheme 2.2.1 Freeman and Kuper disclosed the first Wolff/Cope rearrangement

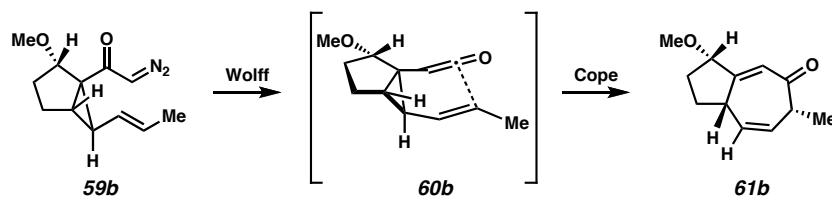


Four decades after Freeman and Kupfer's report, we were struck by the potential of this transformation as a means to access polycyclic scaffolds possessing highly functionalized medium rings.¹⁰ We envisioned that Wolff rearrangement of a structure such as α -diazoketone **59b** would furnish intermediate ketene **60b**. A strain-releasing

ⁱ Unpublished work within this section was executed by Richmond Sarpong and Brian Stoltz, unless otherwise noted.

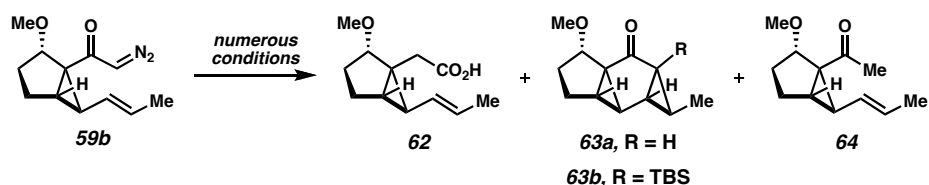
ketene-Cope rearrangement would then afford cycloheptadienone **61b** as the direct product of this tandem Wolff/Cope rearrangement.

Scheme 2.2.2 Targeting a tandem Wolff/Cope rearrangement



Assuming that, once generated, the strained ketene intermediate would undergo thermal rearrangement directly, we began to explore a range of conditions that were commonly employed to induce the Wolff rearrangement. Interestingly, many standard Wolff conditions (including many Lewis acidic conditions) resulted in complex mixtures of products. Product mixtures often included the homologated acid **62**, indicating that the ketene had formed but did not undergo subsequent Cope rearrangement. Additionally, some conditions failed to promote the Wolff rearrangement, resulting in intramolecular cyclopropanation to form tetracycles **63a** (Et₃B, THF, -78 → 23 °C, or Rh₂(OAc)₄, PhH, 100 °C) and **63b** (TBSOTf, *i*-Pr₂NEt, Et₂O, 0 → 23 °C), or diazotization to generate methyl ketone **64**.

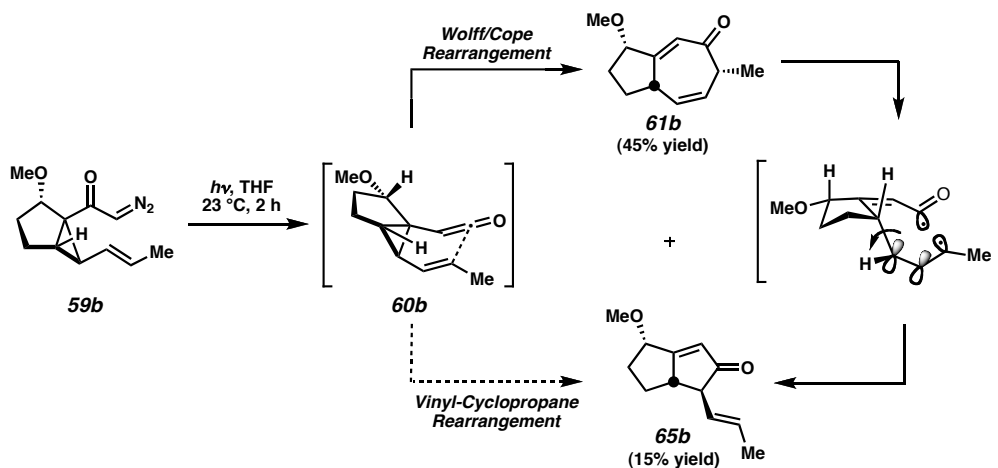
Scheme 2.2.3 Competing reactions of α-diazoketones



We were encouraged by the discovery of photolytic conditions that provided cycloheptadienone **61b** as a single diastereomer, albeit in modest yields, with vinyl cyclopentenone **65b** as a byproduct. Photolysis of α-diazoketone **59b** in anhydrous THF

over 2 h generated cycloheptadieneone **61b** in 45% isolated yield with approximately 15% yield of vinyl cyclopentenone **65b**.¹¹

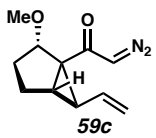
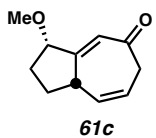
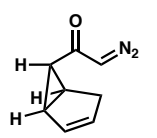
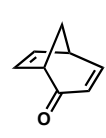
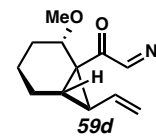
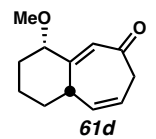
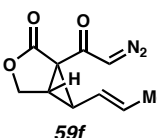
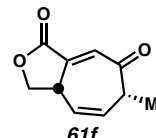
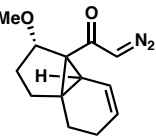
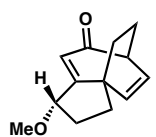
Scheme 2.2.4 Unexpected formation of vinyl cyclopentenone



The unanticipated formation of vinyl cyclopentenone **65b** can be rationalized through a vinyl cyclopropane rearrangement of ketene **60b**. Alternatively, the initial Wolff/Cope product **61b** can undergo a Norrish Type I fragmentation,¹² and a subsequent intramolecular recombination of the transient acyl and allyl radicals as a net 1,3-acyl migration.

Suspecting the radical fragmentation pathway as the most likely cause of by-product formation, we shortened the time over which the reaction was exposed to light. Indeed, with shorter reaction times, photolytic conditions deliver simple [5–7]- as well as [6–7]-fused Wolff/Cope products in good yields (Table 2.2.1). To our delight, employing the more complex [5–3–6]-fused **59d** resulted in formation of the structurally dense polycyclic **61d** in excellent yield. Photolysis of the Freeman and Kuper substrate **59a** at 254 nm provides bridged **61a** in 64% yield. Finally, irradiation of lactone **59e** with a medium pressure mercury lamp, forms lactone-fused **61e**, albeit in a modest 33% yield.

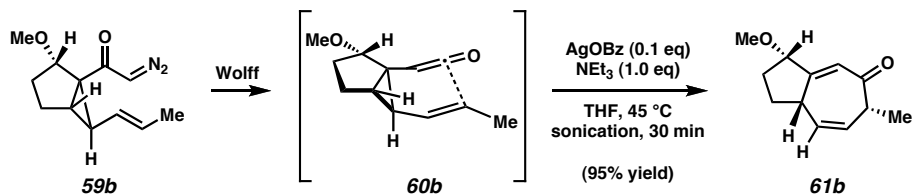
Table 2.2.1 Substrate scope for the photochemical Wolff/Cope rearrangement

entry ^a	substrate	product	yield ^b	entry ^a	substrate	product	yield ^b
1.			80	4.			64
2.			88	5. ^c			33
3.			94				

^a Conditions: hv (254 nm), THF, 23 °C. ^b Percent isolated yield. ^c Performed with a 450 W medium-pressure Hg lamp in THF at 40 °C.

During the course of our investigations, we found that modification of the Montero conditions for ketene formation to include sonication at elevated temperatures cleanly effected the desired Wolff/Cope rearrangement.¹³ Thus, when **59b** was sonicated for 30 minutes at 45 °C in THF with triethylamine and silver benzoate, cycloheptadiene **61b** was isolated in 95% yield.

Scheme 2.2.5 Sonochemical Wolff/Cope conditions



The modified Montero conditions for the Wolff/Cope rearrangement are both mild and general (Table 2.2.2). These conditions effect clean rearrangement of substrates containing methyl, PMB, MOM and enol ethers (entries 1–3). Both terminal and internal olefin substitution are tolerated (entries 1–11). Sterically encumbered substrate **59e**

undergoes sonochemical Wolff/Cope rearrangement, though the yield is reduced relative to the photochemical reaction in this case (entry 7).

Table 2.2.2 Substrate scope for the sonochemical Wolff/Cope rearrangement

entry	substrate	product	conditions ^a	yield ^b	entry	substrate	product	conditions ^a	yield ^b	
1.			R		6.					
2.			Me	B	95	7.			A	94
3.			MOM	B	88			B	76	
	<i>59b, g, h</i>	<i>61b, g, h</i>	PMB	B	92					
4.				B	98	8.			A	64
	<i>59i</i>	<i>61i</i>			9.			B	0	
5.				B	98	10.			A ^c	33
	<i>59j</i>	<i>61j</i>			11.			B	0	

^a Condition A: hv (254 nm), THF, 23 °C. Condition B: AgOBz (0.1 equiv), Et₃N (1.0 equiv), THF, 45 °C, sonication. ^b Percent isolated yield. ^c Performed with a 450 W medium-pressure Hg lamp in THF at 40 °C.

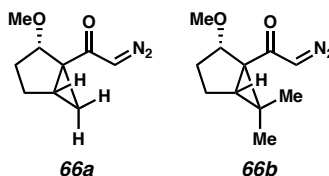
While broadly applicable, the modified Montero conditions did not effect Wolff/Cope rearrangement of all substrates. We were surprised to find that both the Freeman and Kuper substrate (entry 9) and the lactone substrate (entry 11) did not undergo rearrangement under these conditions. The reasons for this lack of reactivity remain unclear.

2.2.2 Investigation of the Wolff/Cope/Acyl Shift Reaction

Once conditions were developed to provide Wolff/Cope products selectively, we sought to confirm the mechanism of vinyl cyclopentenone **65b** formation. Indeed, we found that independent photolysis of pure cycloheptadiene **61b** furnished a vinyl

cyclopentenone **65b**, as the exclusive product. Notably, fused bicyclo-[3.3.0]-octane **65b** forms as a single diastereomer. Two simple substrates have been prepared with the idea of effecting a tandem Wolff/vinyl cyclopropane rearrangement (e.g., **66a** and **66b**, Figure 2.2.2). Neither of these substrates participate in a tandem Wolff/vinyl cyclopropane rearrangement under photolytic conditions. While the vinyl cyclopropane mechanism cannot be excluded, these results imply that the formal 1,3-acyl shift mechanism is operative in the formation of byproduct **65b**.

Figure 2.2.2 Substrates that fail to undergo a Wolff/vinyl cyclopropane rearrangement



On prolonged exposure, photolytic conditions promote the Norrish Type I fragmentation. Additionally, the modified Montero conditions promote rearrangement with a net 1,3-acyl shift in some cases. The scope of this transformation, including both photochemical and sonochemical conditions is outlined in Table 2.2.3. This method allows access to α -vinylated enones in a diastereoselective manner. Of particular note is the ability to access an α -quaternary, α -vinylated enone (entry 4). Additionally, for some substrates, cross-conjugated cyclopentadienone products form (entry 6).

Table 2.2.3 Substrate scope for the Wolff/Cope/1,3-acyl shift sequence

entry	substrate	product	conditions ^a		time	% yield
			R			
1.			Me	B	12 h	72
2.			MOM	B	6 h	69
3.			PMB	B	6 h	75
	59b, g, h	65b, g, h				
4.				B ^b	2 h	80
	59c	65c				
5.				A	0.5 h	57
	59k	65k				
6.				B ^c	6 h	55
	59d	65d		A	0.5 h	72

^a Condition A: AgOBz (0.1 equiv), Et₃N (1.0 equiv), THF, 45 °C, sonication. Condition B: hv (254 nm), THF, 23 °C. ^b Performed with a 450 W medium-pressure Hg lamp in THF at 40 °C. ^c hv (310 nm).

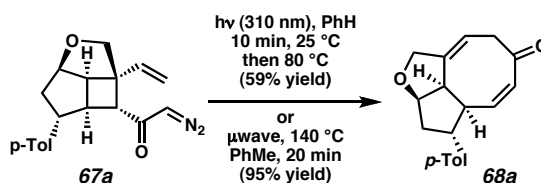
2.2.3 Toward Cyclooctadienones — Cyclobutane Strain Releaseⁱⁱ

Although our initial efforts focused on accessing seven-membered ring systems, we were also interested in the construction of eight-membered ring systems. Accordingly, Wolff/Cope rearrangement of divinylcyclobutane **67a** has been investigated

ⁱⁱ Krout, M. R. Progress Toward the Asymmetric Total Synthesis of Variocolin and Gas-Phase Studies of the Twisted Amide 2-Quinuclidone. Ph.D. Thesis, California Institute of Technology, Pasadena, CA, September 2009. These experiments were carried out as a collaborative effort by Michael R. Krout, Christopher E. Henry, Thomas Jensen, and Brian M. Stoltz.

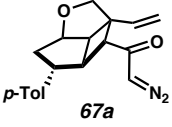
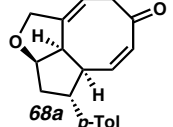
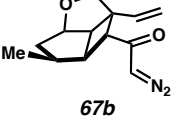
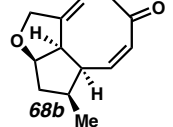
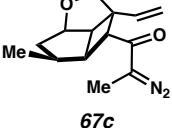
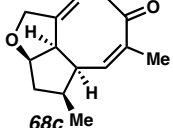
under both sonochemical and photochemical conditions. Unfortunately, neither sonochemical nor photochemical conditions facilitate the Wolff/Cope rearrangement of divinylcyclobutane **67a**. We were gratified to discover that photolysis of cyclobutane **67a** (PhH, 10 min) can be followed by thermolysis at 80 °C to generate cyclooctadienone **68a** in 59% yield. In an effort to improve on this result, we investigated the transformation of cyclobutane **67a** to cyclooctadienone **68a** via microwave irradiation. To our delight, microwave irradiation of cyclobutane **67a** at 140 °C over 20 minutes furnishes cyclooctadienone **68a** in 95% yield.

Scheme 2.2.6 Combined photo/thermochemical and microwave Wolff/Cope conditions



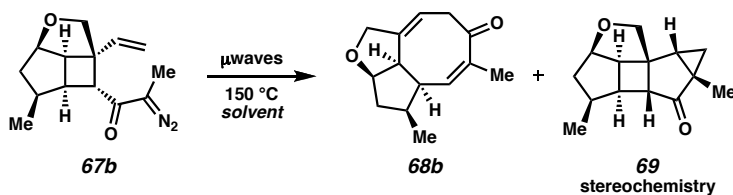
With this result in hand, we sought to extend this reaction to the formation of other cyclooctadienones (Table 2.2.4). A range of aromatic and alkyl substitution is tolerated on the fused cyclopentane ring. Efforts to employ α -methyl- α -diazoketone **67b** revealed that cyclopropanation is again competitive with Wolff rearrangement under these conditions.

Table 2.2.4 Substrate scope for the microwave-promoted Wolff/Cope rearrangement

entry	substrate	product	time (min)	temperature ^a	% yield ^b
1.	 67a	 68a	20	140 °C	95
2.	 67b	 68b	15	160 °C	79
3.	 67c	 68c	10	140 °C	26

^a Conditions: microwave, PhMe. ^b Percent isolated yield.

In an effort to gain access to α -substituted systems, a solvent screen was conducted. Fortunately, the desired Wolff/Cope rearrangement is more competitive in solvents with lower dielectric constants.¹⁴ The optimal yield of desired product was achieved by employing heptane as the solvent at 150 °C in the microwave. These conditions have not yet been tested in the Wolff/Cope rearrangement of cyclopropane-fused substrates.

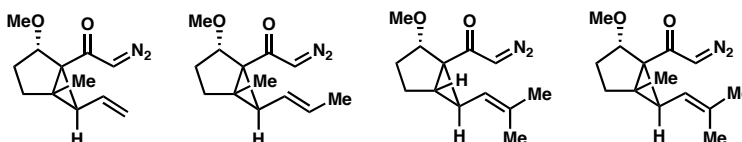
Table 2.2.5 Dielectric effects microwave rearrangements of α -methyl- α -diazoketone

entry ^a	solvent	dielectric constant ^b	68b : 69
1	PhMe	2.41	1.1 : 1
2	EtOAc	6.01	1 : 1.3
3	dioxane	2.1	1 : 1.7
4	DCE	10.43	1 : 2.8
5	MeCN	35.87	1 : 4
6	heptane	1.92	3 : 1

2.2.4 Computational Investigations of Substrate Scope

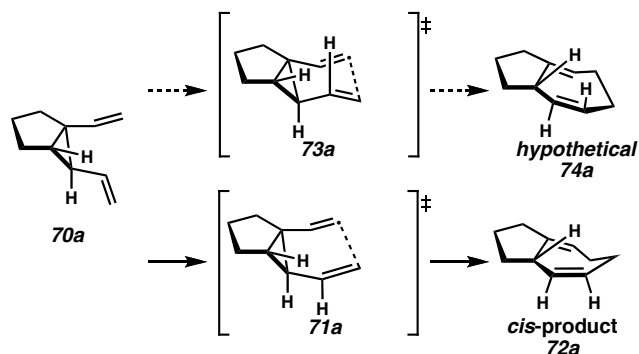
Substrates with terminally disubstituted olefins, or fully substituted carbons at the ring fusion (Figure 2.2.3), fail to undergo Wolff/Cope rearrangement under modified Montero conditions or standard photolytic conditions. Instead, the compounds decompose. To understand why these compounds are not competent Wolff/Cope substrates, computational studies have been undertaken.

Figure 2.2.3 Substrates that fail to undergo a Wolff/Cope rearrangement



When first principal quantum mechanics (B3LYP flavor of unrestricted density functional theory, 6-31G** basis functions)¹⁵ are applied to the Cope rearrangement of a divinylcyclopropane, two transition states can be envisioned for the rearrangement: a boat transition state leading to a stable *cis,cis*-cycloheptadiene (e.g., **70a** → **71a** → **72a**), and an unproductive chair transition state, existing en route to a hypothetical *cis,trans*-cycloheptadiene (e.g., **70a** → **73a** → **74a**). In the simple divinylcyclopropane rearrangement, the productive boat and unproductive chair transitions states differ in free energy by 11.1 kcal/mol. Given this large difference in ΔG^\ddagger , Subtle changes in substrate structure are unlikely to re-order these transition states.

Scheme 2.2.7 Divinylcyclopropane rearrangement pathways



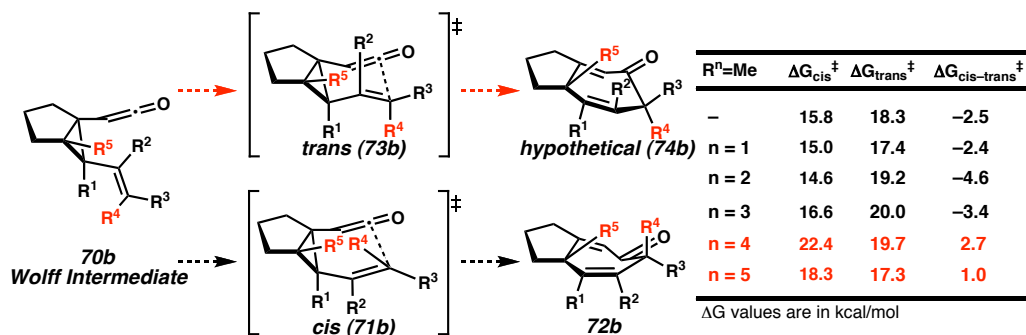
By contrast, activation energies for analogous transition states for the ketene Cope rearrangement differ by a mere 2.5 kcal/mol to favor the boat transition structure with the base substrate (e.g., **70b** → **71b** → **72b**, Table 2.2.6). Given this small energy difference, substrate modifications can re-order these transition states. In our model, positions R⁴ and R⁵ can be separated by as little as 2.13 Å in the boat transition state, potentially leading to destabilizing steric interactions. Methyl substitution of these positions destabilized the boat (**71b**) relative to the chair (**73b**) transition state by as much as 2.7 kcal/mol.

Calculations suggest that the ketene preferentially stabilizes the chair transition state because this transition state has more radical character. The transition state for the Cope rearrangement can be understood as a resonance hybrid of diradical and aromatic forms, with the extent of contribution from each form varying across structures. The diradical pair likely contributes significantly to chair **73b**, but not to boat **71b**, which has more aromatic character. Consequently, radical stabilization by the carbonyl lowers the energy of chair **73b**, but not of boat **71b**.

A chair transition state, leading to *trans*-cycloheptadiene **74b**, while lower in energy than its boat counterpart (**71b**), leads to a prohibitively high energy *trans*-olefin in

a seven-member ring. In accordance with our rationale, *trans*-cycloheptadienones have not been observed. It is likely that given the high energetic barrier for either transition state, a lower energy decomposition pathway is operative.

Table 2.2.6 Effect of methyl substitution on activation energy in ketene Cope reactions



2.3 Conclusions

We have developed the tandem Wolff/Cope rearrangement to address a deficiency in methods to form highly functionalized seven- and eight-membered rings. This work provides direct access to fused [5–7]-, [6–7]-, and [5–8]-systems from vinyl [5–3]-, [6–3]-, and [5–4]-fused α -diazoketones, respectively. We have identified photochemical, sonochemical and microwave conditions that promote this rearrangement. Further, we have established a predictive computational model to identify substrates that are likely to cleanly undergo a Wolff/Cope rearrangement. In the course of these endeavors, we have also discovered a Wolff/Cope/1,3-acyl shift sequence that furnishes vinyl cyclopentenones. Ongoing studies are directed toward further development of the scope of this transformation, and its application to natural product total synthesis.

2.4 Notes and References

- (1) Datta, B. K.; Rashid, M. A.; Datta, S. K.; Sarker, S. D. Viscozulenolic Acid: A Novel Sesquiterpene Acid from *Polygonum viscosum*. *Pharm. Biol.* **2001**, *39*, 198–201.
- (2) May, J. A.; Stoltz, B. M. Non-Carbonyl-Stabilized Metallocarbenoids in Synthesis: The Development of a Tandem Rhodium-Catalyzed Bamford-Stevens/Thermal Aliphatic Claisen Rearrangement Sequence. *J. Am. Chem. Soc.* **2002**, *124*, 12426–12427.
- (3) For an excellent review, see: Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. Cascade Reactions in Total Synthesis. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186.
- (4) (a) Yet, L. Metal-Mediated Synthesis of Medium-Sized Rings. *Chem. Rev.* **2000**, *100*, 2963–3007; (b) Molander, G. A. Diverse Methods for Medium Ring Synthesis. *Acc. Chem. Res.* **1998**, *31*, 603–609.
- (5) Illuminati, G.; Mandolini, L. Ring closure reactions of bifunctional chain molecules. *Acc. Chem. Res.* **1981**, *14*, 95–102.
- (6) Ring fragmentations include the [2+2]/Grob fragmentation, the tandem Kalakovich/oxidation and allyidenecyclopropane rearrangement.
- (7) For recent reviews of ring expansion, see: (a) Katritzky, A. R.; Bobrov, S. The homologation of carbonyl compounds by single carbon insertion reactions. *ARKIVOC*, **2005**, 174–188; (b) Krow, G. R. One carbon ring expansions of bridged bicyclic ketones. *Tetrahedron* **1987**, *43*, 3–38. For a recent advance in ring expansion, see: (c) Hashimoto, T.; Naganawa, Y.; Maruoka, K. Stereoselective Construction of Seven-Membered Rings with an All-Carbon Quaternary Center by

- Direct Tiffeneau–Demjanov-type Ring Expansion. *J. Am. Chem. Soc.* **2009**, *131*, 6614–6617.
- (8) For recent reviews of transition metal-catalyzed cycloadditions in synthesis, see: (a) Battiste, M. A.; Pelphrey, P. M.; Wright, D. L. The Cycloaddition Strategy for the Synthesis of Natural Products Containing Carbocyclic Seven-Membered Rings. *Chem.-Eur. J.* **2006**, *12*, 3438–3447; (b) Wender, P. A.; Bi, F. C.; Gamber, G. G.; Gosselin, F.; Bubbard, R. D.; Scanio, M. J. C.; Sun, R.; Williams, T. J.; Zhang, L. Toward ideal synthesis. New transition metal-catalyzed reactions inspired by novel medicinal leads. *Pure Appl. Chem.* **2002**, *74*, 25–31.
- (9) Freeman, P. K.; Kuper, D. G. Synthesis of Bicyclo[3.2.1] octa-3,6-Dien-2-One: An Unusual Valence Isomerisation. *Chem. Ind.* **1965**, 424–425.
- (10) (a) Sarpong, R.; Su, J. T.; Stoltz, B. M. The Development of a Facile Tandem Wolff/Cope Rearrangement for the Synthesis of Fused Carbocyclic Skeletons. *J. Am. Chem. Soc.* **2003**, *125*, 13624–13625; (b) Su, J. T.; Sarpong, R.; Stoltz, B. M.; Goddard, W. A., III Substituent Effects and Nearly Degenerate Transition States: Rational Design of Substrates for the Tandem Wolff–Cope Reaction. *J. Am. Chem. Soc.* **2004**, *126*, 24–25.
- (11) This photolysis was carried out with a medium pressure Hanovia Hg lamp with a pyrex filter, at 23 °C.
- (12) For general reviews of Norrish Type I fragmentations, see: (a) Chapman, O. L.; Weiss, D. S. Photochemistry of Cyclic Ketones. *Org. Photochem.* **1973**, *3*, 197–

- 277; (b) Horspool, W. M. Photolysis of Carbonyl Compounds. *Photochemistry* **1994**, 25, 67–100.
- (13) (a) Winum, J.-Y.; Kamal, M.; Leydet, A.; Roque, J.-P.; Montero, J.-L. Homologation of Carboxylic Acids by Arndt-Eistert Reaction under Ultrasonic Waves. *Tetrahedron Lett.* **1996**, 37, 1781–1782; (b) Müller, A.; Vogt, C.; Sewald, N. Synthesis of Fmoc- β -Homoamino Acids by Ultrasound-Promoted Wolff Rearrangement. *Synthesis* **1998**, 837–841.
- (14) These solvent dielectrics were at 289.15 K, as reported in: Wohlfarth, Ch. *Landolt-Börstein—Group IV Physical Chemistry*. Ed. Lechner, M. D. Springer-Verlag, Berlin Heidelberg, 2008.
- (15) Run with Jaguar 5.0, Schrodinger, L.L.C. Portland, OR, 1991-2003.